Association of Urinary Calcium Excretion with Serum Calcium and Vitamin D Levels

Rathod, A ; Bonny, O ; Guessous, I ; Suter, P M ; Conen, D ; Erne, P ; Binet, I ; Gabutti, L ; Gallino, A ; Muggli, F ; Hayoz, D ; Pechere-Bertschi, A ; Paccaud, F ; Burnier, M ; Bochud, M

Abstract: BACKGROUND AND OBJECTIVES: Population-based data on urinary calcium excretion are scarce. The association of serum calcium and circulating levels of vitamin D [25(OH)D2 or D3] with urinary calcium excretion in men and women from a population-based study was explored. DESIGN, SETTINGS, PARTICIPANTS, MEASUREMENTS: Multivariable linear regression was used to explore factors associated with square root-transformed 24-hour urinary calcium excretion (milligrams per 24 hours) taken as the dependent variable with a focus on month-specific vitamin D tertiles and serum calcium in the Swiss Survey on Salt Study. RESULTS: In total, 624 men and 669 women were studied with mean ages of 49.2 and 47.0 years, respectively (age range=15-95 years). Mean urinary calcium excretion was higher in men than in women (183.05 versus 144.60 mg/24 h; $P<0.001$). In adjusted models, the association (95% confidence interval) of square root urinary calcium excretion with protein-corrected serum calcium was 1.78 (95% confidence interval, 1.21 to 2.34) mg/24 h per milligram per deciliter in women and 0.59 (95% confidence interval, -0.11 to 1.29) mg/24 h per milligram per deciliter in men. Men in the third 25(OH)D3 tertile had higher square root urinary calcium excretion than men in the first tertile (0.99; 95% confidence interval, 0.36 to 1.63 mg/24 h per nanogram per milliliter), and the corresponding association was 0.32 (95% confidence interval, -0.22 to 0.85) mg/24 h per nanogram per milliliter in women. These sex differences were more marked under conditions of high urinary sodium or urea excretions. CONCLUSIONS: There was a positive association of serum calcium with urinary calcium excretion in women but not men. Vitamin 25(OH)D3 was associated with urinary calcium excretion in men but not women. These results suggest important sex differences in the hormonal and dietary control of urinary calcium excretion.

DOI: https://doi.org/10.2215/CJN.12511213

Association of Urinary Calcium Excretion with Serum Calcium and Vitamin D Levels

Anita Rathod, Olivier Bonny, Idris Guessous, Paolo M. Suter, David Conen, Paul Erne, Isabelle Binet, Luca Gabutti, Augusto Gallino, Franco Muggli, Daniel Hayoz, Antoinette Péchère-Bertschi, Fred Paccaud, Michel Burnier, and Murielle Bochud

Abstract

Background and objectives Population-based data on urinary calcium excretion are scarce. The association of serum calcium and circulating levels of vitamin D [25(OH)D_2 or D_3] with urinary calcium excretion in men and women from a population-based study was explored.

Design, settings, participants, & measurements Multivariable linear regression was used to explore factors associated with square root–transformed 24-hour urinary calcium excretion (milligrams per 24 hours) taken as the dependent variable with a focus on month-specific vitamin D tertiles and serum calcium in the Swiss Survey on Salt Study.

Results In total, 624 men and 669 women were studied with mean ages of 49.2 and 47.0 years, respectively (age range=15–95 years). Mean urinary calcium excretion was higher in men than in women (183.05 versus 144.60 mg/24 h; $P<0.001$). In adjusted models, the association (95% confidence interval) of square root urinary calcium excretion with protein–corrected serum calcium was 1.78 (95% confidence interval, 1.21 to 2.34) mg/24 h per milligram per deciliter in women and 0.59 (95% confidence interval, −0.11 to 1.29) mg/24 h per milligram per deciliter in men. Men in the third 25(OH)D_3 tertile had higher square root urinary calcium excretion than men in the first tertile (0.99; 95% confidence interval, 0.36 to 1.63 mg/24 h per nanogram per milliliter), and the corresponding association was 0.32 (95% confidence interval, −0.22 to 0.85) mg/24 h per nanogram per milliliter in women. These sex differences were more marked under conditions of high urinary sodium or urea excretions.

Conclusions There was a positive association of serum calcium with urinary calcium excretion in women but not men. Vitamin 25(OH)D_3 was associated with urinary calcium excretion in men but not women. These results suggest important sex differences in the hormonal and dietary control of urinary calcium excretion.

Clin J Am Soc Nephrol 10: 452–462, 2015. doi: 10.2215/CJN.12511213

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

Correspondence: Prof. Michel Burnier, Service of Nephrology and Hypertension, Lausanne University Hospital, Rue du Bugnon 17, CH-1005 Lausanne, Switzerland, or Prof. Murielle Bochud, Institute of Social and Preventive Medicine, Lausanne University Hospital, Route de la Corniche 10, CH-1010 Lausanne, Switzerland. Email: Michel.Burnier@chuv.ch or Murielle.Bochud@chuv.ch

Introduction

Calcium ions play a key role in several physiologic processes in humans, and variations of plasma levels of calcium (hypo- or hypercalcemia) may have devastating consequences. Tight control of plasma calcium is achieved by complex regulatory mechanisms, including calcium-sensing receptor, and calcitropic hormones, such as vitamin D (1) and parathyroid hormone (PTH) (2, 3). Two distinct sources of vitamin D are known: vitamin D_2 is mainly provided by food, and vitamin D_3 is synthesized *de novo* in the skin (4) and constitutes the major and more potent isoform (5, 6). Both vitamins D_2 and D_3 need to be hydroxylated to best fit in the docking pocket of the vitamin D receptor and transactivate target genes. Active 1,25$(OH)_2$ vitamin D is produced from circulating levels of 25(OH)D (4) by the activity of the 1α-hydroxylase CYP27B1 and further degraded by the activity of CYP24A1 (7). Active 1,25(OH)2D stimulates intestinal calcium absorption and bone resorption and decreases renal calcium excretion.

Urinary calcium results from glomerular filtration of albumin-free plasma calcium and intense calcium reabsorption along the different tubular segments, where regulation by several anticalciuretic factors, such as 1,25$(OH)_2$D, PTH, sex hormones, or dietary factors, is exerted. Increased urinary calcium excretion—hypercalciuria—may, thus, derive from excessive intestinal absorption or increased bone resorption, providing an excessive load to be filtered by the glomerulus, or may be caused by tubular dysfunction and decreased reabsorption.

Hypercalciuria was extensively studied in relation to kidney stone formation (8) and osteoporosis (9, 10). However, population-based data on urinary calcium excretion are scarce, and the relationship between serum calcium and urinary calcium excretion or between circulating 25(OH)D levels and urinary calcium excretion has surprisingly not been fully explored or remains controversial. Indeed, the InChianti Study found a positive association between urinary calcium excretion and circulating 25(OH) vitamin D in men but not in women.

In other studies, urinary calcium excretion was positively associated with 1,25$(OH)_2$ vitamin D_3 in middle-aged men with or without kidney stones. By contrast, Eisner *et al.* (11) found no association between urinary calcium excretion and serum 25(OH) vitamin D. Overall, only few data describe sex-specific associations of urinary calcium excretion with serum calcium or vitamin D.

We investigated the association of 24-hour urinary calcium excretion with circulating vitamin D [25$(OH)D_2$ and/or 25$(OH)D_3$; 25$(OH)D_3$ having a higher level than 25$(OH)D_2$] and serum calcium by sex in a Swiss population-based sample.

Materials and Methods

Source Population

Methods have been described previously (12). Briefly, data were used from the Swiss Survey on Salt Intake (SSS) Study (13) conducted between January of 2010 and March of 2012. The main goal of the study was to assess the mean dietary sodium intake.

The SSS Study is a population-based multicenter study including 1550 people living in the French-, German-, and Italian-speaking parts of Switzerland. Inclusion criteria were that participants had to be above 15 years old, permanent resident of Switzerland, not living in an institution, and able to answer questions in French, Italian, or German. Participants were sampled using eight age (15–29, 30–44, 45–49 and >60 years) and sex strata. Participation rate was 10%.

Participants were informed and gave written consent; the parents or legal representatives of participants <18 years old also gave written consent. The SSS Study fulfilled the tenets of the Declaration of Helsinki and was accepted by the local institutional ethics committees.

Data Collection

Participants answered a questionnaire on sociodemographic variables, alcohol consumption, smoking, and kidney stone status. Resting BP was taken in the sitting position five times at both of two visits with an automatic Omron HEM-907 oscillometric device; a nonfasting blood test was taken, and 24-hour urine was collected (unrestricted diets). Of 1550 participants, 1373 participants had 25(OH) vitamin D levels available, and 80 participants had one or several missing covariates. Blood and urine were analyzed centrally.

Urine and total serum calcium were measured by the *O*-cresolphtalein method. Intra- and interbatch coefficients of variation (CVs) for urinary values were 0.80% and 1.40% for concentrations of 14.60 and 18.41 mg/dl, respectively; 1.20% and 1.60% for concentrations of 6.23 and 6.15 mg/dl, respectively; and 0.90% and 1.40% for concentrations of 11.03 and 10.91 mg/dl, respectively. Intra- and interbatch CVs for serum values were 0.90% and 1.60%, respectively. Total serum proteins were measured by the Biuret reaction (intra- and interbatch CVs were 0.60% and 1.00%, respectively); protein-corrected serum calcium was then calculated (14). Serum 25(OH)D [including vitamin 25$(OH)D_2$ and 25$(OH)D_3$] concentration was measured by liquid chromatography–tandem mass spectrometry (intra- and interbatch CVs were 4% and 8%, respectively) (12,15). Serum urea was measured by the Urease-glutamate deshydrogenase method (intra- and interbatch CVs were 0.80% and 3.40%, respectively). Serum creatinine and urine creatinine were measured by the Jaffé kinetic compensated method (intra- and interbatch CVs of serum values were 0.70% and 2.30%, respectively; intra- and interbatch CVs of urinary values were 2.10% and 2.20% for concentrations of 0.12 and 0.12 mg/dl, respectively; 1.30% and 1.70% for concentrations of 0.21 and 0.20 mg/dl, respectively; and 1.10% and 1.20% for concentrations of 0.60 and 0.58 mg/dl, respectively). Urinary phosphate was determined by the phosphomolybdate method (intra- and interbatch CVs were 0.70% and 1.30% for concentrations of 86.80 and 83.70 mg/dl, respectively, and 0.80% and 1.40% for concentrations of 43.40 and 43.40 mg/dl, respectively). eGFR was calculated with the CKD Epidemiology Collaboration equation (16).

Hypercalciuria was defined as urinary calcium excretion >4 mg/kg per 24 hours (17,18), a definition used in prior studies in adults and children. For all other analyses, urinary calcium excretion was not corrected for body weight, because we wanted to explore the association with body mass index (BMI; weight per height^2 in kilograms per meter^2), and most prior studies did not correct for body weight.

Statistical Analyses

We used Stata 12 (StataCorp LP, College Station, TX) for statistical analyses. Continuous variables were presented as means±95% confidence intervals, and binary variables were presented as numbers of participants and percentages. Differences in means and proportions across groups were tested (and *P* values were reported) using *t* and Pearson chi-squared tests. To satisfy regression assumptions, 24-hour urinary calcium excretion and 24-hour urinary phosphate excretion were square root transformed. Serum 25(OH)D [which included vitamin 25$(OH)D_2$ and 25(OH) D_3] was divided into month-specific tertiles, with the first tertile having the lowest value and the third tertile having the highest value as previously described (12). Dividing vitamin D levels into month-specific tertiles represents the best way to take into account the seasonal variation in vitamin D (19). In the first stage, vitamin D levels are divided into tertiles (separate for each month). In the second stage, the tertiles are combined across 12 months, thereby creating month-specific tertiles.

Multivariable linear regression was used to determine the association between covariates of interest and 24-hour urinary calcium excretion as the dependent variable. We tested *a priori*–selected interaction with sex. We conducted separate analyses by sex, because we found significant sex interactions in the final model, namely serum calcium by sex ($P<0.01$) and 25$(OH)D_{2+3}$ by sex ($P=0.03$). Covariates included age, BMI, mean arterial BP, protein-corrected serum calcium, month-specific tertiles of vitamin D, eGFR, 24-hour urinary phosphate excretion in grams per 24 hours, 24-hour urinary creatinine excretion in milligrams per kilogram per 24 hours, 24-hour urinary volume in liters, alcohol use, smoking, physical activity, menopause, linguistic region, and some drugs related to calcium excretion. Urinary volume and creatinine excretion were included as covariates to take the completeness of urine collection into account. Menopause was divided into pre- and postmenopausal status, and smoking status was divided into current smoker and nonsmoker. Alcohol use was defined as present if participants reported consuming at least one unit of

alcohol (including beer, wine, and/or spirits) during the past 7 days. Physical activity was defined as present if participants reported to have physical activity at least one time per month. Drugs influencing calcium homeostasis were added as covariates, namely calcium supplementation, vitamin D supplementation, diuretics (which included participants taking thiazides diuretics [n=8] and loop diuretics [n=1]), corticoids, bisphosphonate, angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), and thyroid hormone substitution. Contraceptive pills were added into the models for premenopausal women, and hormone replacement therapy was added into the models for postmenopausal women. We present results for unadjusted (model 1) and fully adjusted (model 2) models. The fully adjusted model included as covariate variables having a P value <0.10 in either men and/or women while forcing linguistic region, ARB, ACEI, diuretics, and vitamin D supplementation into the model. We used a cutoff of 0.05 for statistical significance for main covariates and a cutoff of 0.10 for interaction terms. Analyses were restricted to participants with all variables of interests. We conducted sensitivity analyses to explore whether urinary sodium/potassium/urea excretion and caffeine intake had a significant effect on the observed associations and also, whether excluding participants with self-reported kidney stone status (with no significant stone by serum calcium [P>0.60] or 25(OH)D_{2+3} [P>0.60] interactions in both sexes), those with potential incomplete urine collection (defined as urine volume below 500 ml or urinary creatinine excretion below sex-specific percentile 5 [13.64 mg/kg per 24 hours in men and 9.28 mg/kg per 24 hours in women]), those with hypercalcemia (defined as protein-corrected serum calcium above the 99th percentile: >10.41 mg/dl for men and >10.62 mg/dl for women), those with eGFR<60 ml/min per 1.73 m^2, those taking calcium and/or vitamin D supplements, or those taking antihypertensive treatment influenced the results. We also explored whether vitamin D modified the association of urinary calcium excretion with urinary phosphate excretion (by including a multiplicative interaction term in the model) or if it confounded this association. To explore a potential effect modification by dietary factors, we conducted stratified analyses by high versus low urinary sodium, potassium, and urea excretions as well as reported alcohol intake.

Results

We included in this analysis 1293 participants with no missing values for all variables of interest (83% of the overall sample). The distributions of 24-hour urinary calcium excretion in this population-based sample were rightly skewed in both men and women (Figure 1A). After adjusting for weight, the distribution became similar in men and women (Figure 1B).

Protein-corrected serum calcium was similar in men and women (Table 1). Mean (SD) serum vitamin D [25(OH)D_{2+3}] values in month-specific tertiles were 14.84 (±5.70), 22.86 (±4.92), and 33.52 (±8.34) in men and 14.87 (±5.32), 23.71 (±5.14), and 34.93 (±7.83) in women for tertiles 1–3, respectively. Men had significantly higher 24-hour urinary calcium excretion than women but not when adjusted for body weight. This observed sex difference, therefore, merely reflects a difference in body weight. Levels of 25(OH)D_3 were much higher than levels of 25(OH)D_2 independent of sex. The distributions of 25(OH)D_2 and 25(OH)D_3 are shown in Supplemental Figure 1.

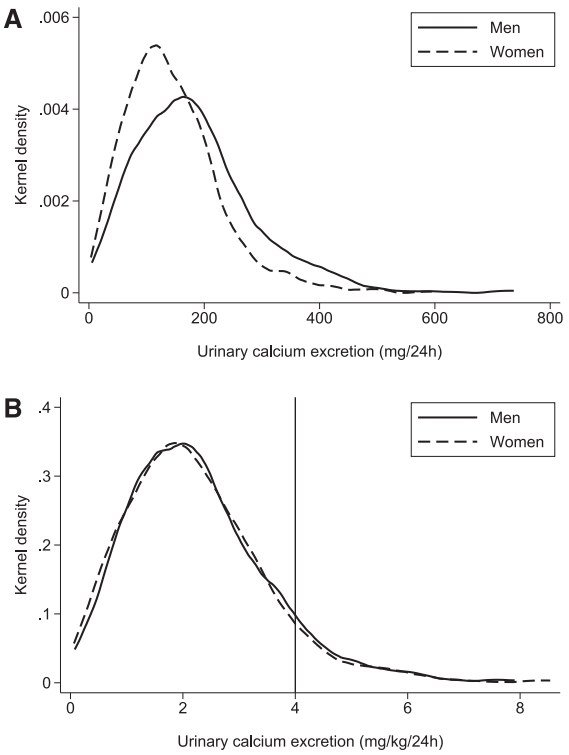

Figure 1. | Distribution of 24-hour urinary calcium excretion in. (A) Milligrams per 24 hours and (B) milligrams per kilogram per 24 hours by sex. Distribution is illustrated by Kernel density.

In women, but not in men, serum calcium was significantly associated with urinary calcium excretion in multivariable models (Table 2, Supplemental Table 1). In men, but not in women, urinary calcium excretion was associated with month-specific 25(OH)D_{2+3} tertiles. These associations were independent of urinary sodium excretion, urinary potassium excretion, urinary urea excretion, caffeine intake (not shown here), kidney stone status, urine collection, eGFR<60 ml/min per 1.73 m^2, hypercalcemia (>10.41 mg/dl for men and >10.62 mg/dl for women), vitamin D and calcium supplementation, and antihypertensive treatment. ACEIs were negatively associated with urinary calcium excretion in men and women. ARBs were strongly negatively associated with urinary calcium in women, with weaker negative associations in men. In our data, vitamin D did not modify the association of urinary calcium excretion with urinary phosphate excretion (no effect modification and no confounding effect). Seasonal variations in urinary calcium excretion were minor and only occurred in men, with a significantly lower excretion in winter compared with summer (not shown here).

When differentiating 25(OH)D_2 and 25(OH)D_3, urinary calcium excretion remained associated with serum calcium in women but not in men (Table 3, Supplemental Table 2). In men, urinary calcium excretion was associated with 25(OH)D_3 month-specific tertiles but not 25(OH)D_2. In women, urinary calcium excretion was not associated

Table 1. Participants' characteristics by sex

Participants' Characteristics	Men (*n*=624)	Women (*n*=669)	*P* Value
Urinary calcium excretion (mg/24 h)	183.05 (±104.18)	144.60 (±83.14)	<0.001
Urinary calcium excretion (mg/kg per 24 h)	2.27 (±1.25)	2.23 (±1.25)	0.53
Age (yr)	49.2 (±18.1)	47.0 (±17.9)	0.02
French-speaking region	199 (31.8%)	218 (32.5%)	
German-speaking region	339 (54.3%)	358 (53.5%)	
Italian-speaking region	86 (13.7%)	93 (13.9%)	0.95
Menopause	—	295 (44.1%)	NA
Alcohol user	535 (85.7%)	443 (66.2%)	<0.001
Smoking	110 (17.1%)	107 (15.9%)	0.43
Physical activity >1 time/mo	314 (50.3%)	324 (48.3%)	0.49
Self-reported kidney stone	63 (10.1%)	48 (7.2%)	0.06
Body mass index (kg/m^2)	26.1 (±4.2)	24.4 (±4.6)	<0.001
Mean arterial BP (mmHg)	94.0 (±10.6)	87.7 (±10.4)	<0.001
Protein-corrected serum calcium (mg/dl)	9.22 (±0.38)	9.23 (±0.40)	0.57
eGFR (ml/min per 1.73 m^2)	89.7 (±19.0)	90.2 (±19.5)	0.58
Serum urea (mg/dl)	36.23 (±12.69)	30.32 (±8.69)	<0.001
25(OH)D$_{2+3}$ month-specific (ng/ml)			0.03
Tertile 1	14.84 (±5.70)	14.87 (±5.32)	
Tertile 2	22.86 (±4.92)	23.71 (±5.14)	
Tertile 3	33.52 (±8.34)	34.93 (±7.83)	
25(OH)D$_2$ month-specific (ng/ml)			0.24
Tertile 1	0.42 (±0.13)	0.44 (±0.13)	
Tertile 2	0.72 (±0.12)	0.72 (±0.12)	
Tertile 3	1.25 (±0.53)	1.25 (±0.62)	
25(OH)D$_3$ month-specific (ng/ml)			0.07
Tertile 1	14.06 (±5.64)	14.31 (±5.47)	
Tertile 2	22.10 (±5.04)	23.09 (±5.06)	
Tertile 3	32.71 (±8.46)	34.46 (±7.75)	
Urinary creatinine excretion (mg/kg per 24 h)	21.54 (±4.88)	16.91 (±4.53)	<0.001
24-h Urinary volume (L)	1.7 (1.2–2.3)	1.9 (1.2–2.5)	0.05
Urinary phosphate excretion (g/24 h)	1.00 (±0.17)	0.82 (±0.15)	<0.001
Angiotensin-converting enzyme inhibitor	38 (6.0%)	23 (3.4%)	0.02
Angiotensin receptor blocker	65 (10.4%)	41 (6.1%)	<0.01
Calcium supplementation	6 (0.9%)	39 (5.8%)	<0.001
Vitamin D supplementation	6 (0.9%)	12 (1.7%)	0.20
Corticoid	1 (0.1%)	0	0.48
Thyroid hormone	4 (0.6%)	28 (4.1%)	<0.001
Diuretics	5 (0.8%)	4 (0.6%)	0.66
Oral contraception	—	85 (12.7%)	NA
Hormonal substitution	—	46 (6.8%)	NA

Data are means (±SDs), medians (interquartile ranges), and *n* (percentages) unless otherwise specified. eGFR was calculated by the CKD Epidemiology Collaboration equation. NA, not available.

with month-specific 25(OH)D tertiles, regardless of the vitamin D subtype.

Figure 2 illustrates the sex differences in the adjusted association of urinary calcium excretion with protein-corrected serum calcium and 25(OH)D$_{2+3}$.

Stratified analyses by low versus high urinary sodium, potassium, and urea excretions and alcohol intake can be found in Supplemental Table 3. These dietary factors did not significantly modify the associations of interest in men. By contrast, the associations of urinary calcium excretion with serum calcium and vitamin D tertiles differed between high versus low urinary sodium excretion strata in women. Furthermore, the sex-by–serum calcium and sex-by–vitamin D interactions (for their effects on urinary calcium excretion) were more significant under conditions of high urinary sodium excretion and high urinary urea excretion (Supplemental Table 4).

We found no significant association of hypercalciuria with age, BMI categories, or vitamin D tertiles (Figure 3). In women, hypercalciuria prevalence was positively associated with tertiles of serum calcium (4.7%–11.4%; *P*=0.02). The prevalence values of hypercalciuria were 9.0% and 8.1% in men and women, respectively; 8.4% and 7.4% in nonstone-forming men and women, respectively; and 14.3% and 16.7% in stone-forming men and women, respectively.

Discussion

In this cross-sectional population-based study, 24-hour urinary calcium excretion was strongly and positively associated with serum calcium in women but not men. By contrast, 24-hour urinary calcium excretion was associated positively with month-specific vitamin D tertiles in men but not women.

Table 2. Factors associated with square root–transformed urinary calcium excretion (milligrams per 24 hours) by sex

	Men				Women			
	Model 1		Model 2		Model 1		Model 2	
Independent Variables	ΔSquare Root Urinary Calcium (95% CI)	*P* Value	ΔSquare Root Urinary Calcium (95% CI)	*P* Value	ΔSquare Root Urinary Calcium (95% CI)	*P* Value	ΔSquare Root Urinary Calcium (95% CI)	*P* Value
Age (per 10 yr)	−0.28 (−0.45 to −0.12)	0.001	0.39 (0.15 to 0.63)	0.002	−0.11 (−0.25 to 0.04)	0.14	0.36 (0.15 to 0.57)	0.001
Body mass index (kg/m^2)	0.15 (0.08 to 0.22)	<0.001	0.16 (0.07 to 0.24)	<0.001	0.07 (0.02 to 0.13)	0.01	0.10 (0.04 to 0.16)	0.001
Mean BP (mmHg)	0.02 (−0.01 to 0.05)	0.10	0.02 (−0.01 to 0.04)	0.24	0.03 (0.01 to 0.05)	0.02	0.02 (−0.01 to 0.05)	0.07
Serum corrected calcium (mg/dl)	0.41 (−0.38 to 1.20)	0.31	0.59 (−0.11 to 1.29)	0.10	1.54 (0.91 to 2.18)	<0.001	1.78 (1.21 to 2.34)	<0.001
Vitamin D tertile 1 (ng/ml)	Reference		Reference		Reference		Reference	
Vitamin D tertile 2 (ng/ml)	0.58 (−0.13 to 1.30)	0.11	0.53 (−0.07 to 1.13)	0.08	0.50 (−0.14 to 1.15)	0.13	0.51 (−0.03 to 1.05)	0.07
Vitamin D tertile 3 (ng/ml)	1.28 (0.54 to 2.03)	0.001	1.08 (0.44 to 1.72)	0.001	0.30 (−0.33 to 0.92)	0.36	0.30 (−0.24 to 0.85)	0.27
Urea (mg/dl)	−0.03 (−0.06 to −0.01)	0.004	NI		−0.01 (−0.03 to 0.03)	0.84	NI	
eGFR (ml/min per 1.73 m^2)	0.44 (0.29 to 0.60)	<0.001	0.54 (0.34 to 0.74)	<0.001	0.16 (0.03 to 0.30)	0.02	0.36 (0.19 to 0.52)	<0.001
Urinary phosphate (g/24 h)	11.26 (9.74 to 12.79)	<0.001	6.81 (4.71 to 8.90)	<0.001	10.34 (8.79 to 11.89)	<0.001	6.76 (4.90 to 8.62)	<0.001
Creatininuria (mg/kg per 24 h)	0.26 (0.20 to 0.31)	<0.001	0.15 (0.08 to 0.23)	<0.001	0.24 (0.18 to 0.29)	<0.001	0.20 (0.13 to 0.27)	<0.001
Urinary volume (L)	0.77 (0.43 to 1.10)	<0.001	0.52 (0.22 to 0.81)	0.001	0.81 (0.54 to 1.09)	<0.001	0.35 (0.10 to 0.60)	<0.01
Alcohol use	1.33 (0.47 to 2.18)	0.002	0.60 (−0.13 to 1.32)	0.11	1.05 (0.51 to 1.59)	<0.001	0.65 (0.19 to 1.11)	<0.01
Smoking	1.46 (0.67 to 2.24)	<0.001	0.74 (0.08 to 1.41)	0.03	0.82 (0.11 to 1.52)	0.02	0.59 (−0.01 to 1.18)	0.05
Physical activity	0.20 (−0.40 to 0.80)	0.51	NI		0.29 (−0.23 to 0.81)	0.27	NI	
French-speaking region	Reference		Reference		Reference	—	Reference	
German-speaking region	−0.40 (−1.07 to 0.27)	0.24	−0.78 (−1.36 to −0.21)	<0.01	−0.18 (−0.76 to 0.39)	0.54	−0.51 (−1.01 to −0.01)	0.05
Italian-speaking region	−0.15 (−1.12 to 0.82)	0.76	−0.48 (−1.29 to 0.33)	0.25	−0.27 (−1.10 to 0.56)	0.52	−0.14 (−0.84 to 0.55)	0.69
Menopause	—		—		−0.08 (−0.60 to 0.44)	0.77	NI	
Drugs								
Calcium supplementation	−2.61 (−5.70 to 0.47)	0.10	−0.12 (−2.83 to 2.60)	0.93	0.10 (−1.00 to 1.21)	0.86	1.41 (0.42 to 2.41)	<0.01
Vitamin D supplementation	−1.46 (−4.55 to 1.63)	0.35	−1.41 (−4.12 to 1.30)	0.31	−0.69 (−2.64 to 1.26)	0.49	−0.79 (−2.41 to 0.82)	0.33
Diuretics	−3.04 (−6.42 to 0.33)	0.08	−1.22 (−4.06 to 1.62)	0.40	−2.45 (−5.80 to 0.91)	0.15	−1.14 (−3.92 to 1.64)	0.42

Table 2. (Continued)

Independent Variables	Men				Women			
	Model 1		Model 2		Model 1		Model 2	
	ΔSquare Root Urinary Calcium (95% CI)	*P* Value	ΔSquare Root Urinary Calcium (95% CI)	*P* Value	ΔSquare Root Urinary Calcium (95% CI)	*P* Value	ΔSquare Root Urinary Calcium (95% CI)	*P* Value
Corticoids	−1.26 (−8.80 to 6.28)	0.74	NI		0		*NI*	
ACEI	−1.44 (−2.69 to −0.18)	0.03	−1.12 (−2.22 to −0.02)	0.05	−1.43 (−2.84 to −0.01)	0.05	−1.37 (−2.60 to −0.15)	0.03
ARB	−0.86 (−1.85 to 0.12)	0.09	−0.81 (−1.70 to 0.08)	0.08	−2.03 (−3.10 to −0.96)	<0.001	−1.93 (−2.88 to −0.98)	<0.001
Thyroid hormone substitution	−2.02 (−5.80 to 1.75)	0.29	NI		0.83 (−0.46 to 2.12)	0.21	NI	
Oral contraceptive pill	—		—		−0.86 (−1.63 to −0.08)	0.03	NI	
Estrogen hormone substitution	—		—		−0.05 (−1.19 to 1.09)	0.93	NI	

This information is the result of a multivariable linear regression. Urinary calcium excretion used as the dependent variable (in milligrams per 24 hours) was square root–transformed to better achieve a normal distribution of the residuals. Model 1 is the unadjusted model. Model 2 is the fully adjusted model (we kept covariates with a *P* value<0.10 and forced age, linguistic region, diuretics, and calcium and vitamin D supplementations into the model). Vitamin D includes $25(OH)D_{2+3}$ expressed in month-specific tertiles. eGFR was calculated by the CKD Epidemiology Collaboration equation. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; 95% CI, 95% confidence interval; NI, not included in the multivariate linear regression.

Table 3. Association of 25(OH)D and protein–corrected serum calcium with square root–transformed urinary calcium excretion (milligrams per 24 hours) by sex

Independent Variables	Men				Women			
	Model 1		Model 2		Model 1		Model 2	
	ΔSquare Root Urinary Calcium (95% CI)	*P* Value	ΔSquare Root Urinary Calcium (95% CI)	*P* Value	ΔSquare Root Urinary Calcium (95% CI)	*P* Value	ΔSquare Root Urinary Calcium (95% CI)	*P* Value
Models including only D_2								
Vitamin D_2, tertile 1 (ng/ml)	Reference		Reference		Reference		Reference	
Vitamin D_2, tertile 2 (ng/ml)	0.27 (−0.46 to 1.00)	0.47	0.15 (−0.45 to 0.76)	0.62	0.09 (−0.55 to 0.73)	0.78	0.08 (−0.46 to 0.61)	0.79
Vitamin D_2, tertile 3 (ng/ml)	0.03 (−0.71 to 0.77)	0.93	0.36 (−0.26 to 0.98)	0.25	−0.54 (−1.17 to 0.10)	0.10	−0.01 (−0.55 to 0.53)	0.98
Serum calcium in model 2 (mg/dl)	—		0.68 (−0.03 to 1.38)	0.06	—		1.77 (1.20 to 2.33)	<0.001
Models including only D_3								
Vitamin D_3, tertile 1 (ng/ml)	Reference		Reference		Reference		Reference	
Vitamin D_3, tertile 2 (ng/ml)	0.73 (0.02 to 1.45)	0.04	0.53 (−0.08 to 1.13)	0.09	0.58 (−0.07 to 1.22)	0.08	0.44 (−0.11 to 0.98)	0.12
Vitamin D_3, tertile 3 (ng/ml)	1.35 (0.60 to 2.09)	<0.001	0.99 (0.36 to 1.63)	0.002	0.36 (−0.26 to 0.98)	0.25	0.32 (−0.22 to 0.85)	0.25
Serum calcium in model 2 (mg/dl)	—		0.58 (−0.12 to 1.28)	0.10	—		1.77 (1.21 to 2.34)	<0.001
Models including only D_{2+3}								
Vitamin D_{2+3}, tertile 1 (ng/ml)	Reference		Reference		Reference		Reference	
Vitamin D_{2+3}, tertile 2 (ng/ml)	0.58 (−0.13 to 1.30)	0.10	0.53 (−0.07 to 1.13)	0.08	0.50 (−0.14 to 1.15)	0.12	0.51 (−0.03 to 1.05)	0.06
Vitamin D_{2+3}, tertile 3 (ng/ml)	1.28 (0.54 to 2.03)	0.001	1.08 (0.44 to 1.71)	0.001	0.29 (−0.33 to 0.92)	0.35	0.30 (−0.24 to 0.85)	0.27
Serum calcium in model 2 (mg/dl)	—		0.59 (−0.10 to 1.29)	0.09	—		1.78 (1.21 to 2.34)	<0.001
Models including D_2 and D_3								
Vitamin D_2, tertile 1 (ng/ml)	Reference		Reference		Reference		Reference	
Vitamin D_2, tertile 2 (ng/ml)	0.23 (−0.49 to 0.96)	0.53	0.12 (−0.48 to 0.72)	0.70	0.11 (−0.53 to 0.75)	0.73	0.08 (−0.46 to 0.62)	0.78
Vitamin D_2, tertile 3 (ng/ml)	0.04 (−0.69 to 0.77)	0.92	0.35 (−0.27 to 0.96)	0.27	−0.50 (−1.13 to 0.14)	0.13	0.02 (−0.52 to 0.56)	0.94
Vitamin D_3, tertile 1 (ng/ml)	Reference		Reference		Reference		Reference	
Vitamin D_3, tertile 2 (ng/ml)	0.71 (−0.01 to 1.43)	0.05	0.52 (−0.09 to 1.12)	0.09	0.54 (−0.10 to 1.19)	0.10	0.44 (−0.11 to 0.98)	0.12
Vitamin D_3, tertile 3 (ng/ml)	1.34 (0.59 to 2.08)	<0.001	0.99 (0.35 to 1.63)	0.002	0.32 (−0.31 to 0.94)	0.32	0.31 (−0.23 to 0.85)	0.26
Serum calcium in model 2 (mg/dl)	—		0.59 (−0.11 to 1.29)	0.10	—		1.77 (1.21 to 2.34)	<0.001

This information is the result of a multivariable linear regression. Urinary calcium excretion used as the dependent variable (in milligrams per 24 hours) was square root–transformed to better achieve a normal distribution of the residuals. Model 1 is the unadjusted model. Model 2 is the fully adjusted model (we kept covariates with a *P* value <0.10 and forced age, linguistic region, diuretics, and calcium and vitamin D supplementations into the model). Vitamin D_2 is vitamin D included as 25(OH)D_2 into the models. Vitamin D_3 is vitamin D included as 25(OH)D_3 into the models. Serum 25(OH)D_2, 25(OH)D_3, and 25(OH)D_{2+3} were divided into month-specific tertiles, with the first tertile having the lowest value and the third tertile having the highest value. Serum calcium is serum protein-corrected calcium. 95% CI, 95% confidence interval.

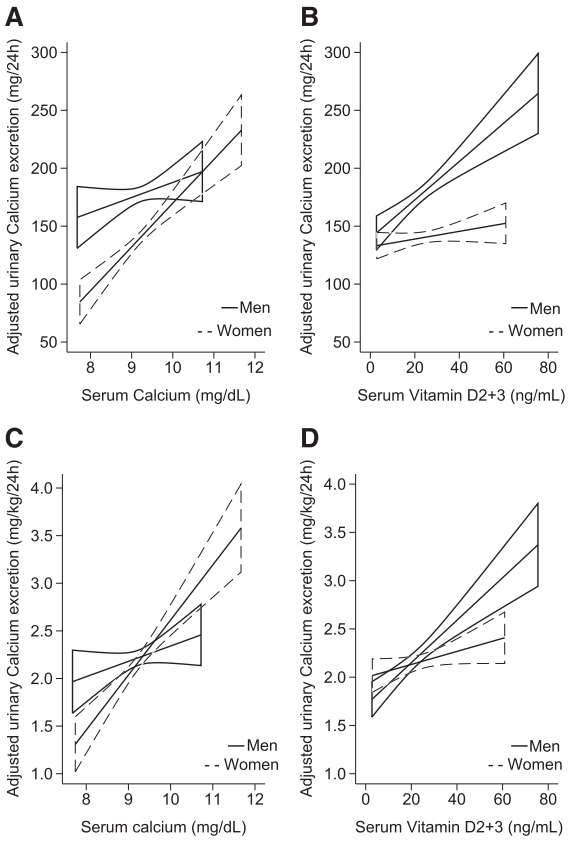

Figure 2. | Relationship of 24-hour urinary calcium excretion with protein-corrected serum calcium and serum 25(OH)D_{2+3} by sex. (A) Relationship of square root–transformed adjusted urinary calcium excretion (milligrams per 24 hours) with protein-corrected serum calcium. (B) Relationship of square root–transformed adjusted urinary calcium excretion (milligrams per 24 hours) with vitamin 25(OH)D_{2+3}. (C) Relationship of square root–transformed adjusted urinary calcium excretion (milligrams per kilogram per 24 hours adjusted for weight) with protein-corrected serum calcium. (D) Relationship of square root–transformed adjusted urinary calcium excretion (milligrams per kilogram per 24 hours adjusted for weight) with vitamin 25(OH)D_{2+3}. We used separate models for men and women. Models were adjusted for age, body mass index, mean arterial BP, eGFR, 24-hour urinary phosphate excretion, 24-hour urinary creatinine excretion, 24-hour urinary volume, alcohol use, smoking status, linguistic region, and some drugs related to calcium excretion: angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, calcium and vitamin D supplementation, diuretics, (B and D) protein-corrected serum calcium, and (A and C) 25(OH)D_{2+3}. The graphs show linear fits and 95% confidence intervals for adjusted residuals.

The association of urinary calcium excretion with vitamin D was mainly explained by 25(OH)D_3 and not 25(OH)D_2. These results suggest important sex differences in the relationships of urinary calcium excretion with serum calcium and vitamin D levels in the population.

Serum calcium was associated positively with urinary calcium excretion in women independent of menopausal status and hormonal supplementation. No such clear-cut positive association was observed in men. Our results contrast with those of prior smaller-sized studies. In the InChianti Study (n=595) (10), an association between serum calcium and 24-hour urinary calcium excretion was observed in men but not women. Peacock *et al.* (20) found a positive association between serum calcium load and urinary calcium excretion in 72 men and women. Both studies differ from our study in many ways, including differences in sample size, recruitment, inclusion criteria, and covariates considered, which may explain these discrepancies. A possible explanation for the observed sex differences could be the role of sex hormones. In animal studies, estrogen was found to stimulate calcium reabsorption in the kidney (21), whereas testosterone was found to inhibit it (22). Alternatively, CYP24A1 or CYP27B1 activity might differ in men and women (23). Estrogens seem to suppress CYP24A1 transcripts and therefore, induce the accumulation of 1,25(OH)2D_3. Another explanation for the observed sex differences is diet. In women only, we found that urinary calcium excretion was more strongly associated with serum calcium under conditions of high compared with low salt intake. Interestingly, the association of urinary calcium excretion with serum calcium was similar in men and women under conditions of low urinary sodium excretion and low urea excretion, which suggests that dietary salt and protein intakes may explain, as least partly, the observed sex differences.

In this study, men in the highest month-specific 25(OH)D_{2+3} tertile excreted a higher level of urinary calcium compared with men in the lowest tertile, whereas no such association was found in women. These results are similar for 25(OH)D_3 alone but not for 25(OH)D_2. The lack of association between 25(OH)D_2 and urinary calcium excretion could be explained by the very low circulating level of vitamin D_2 compared with D_3 in this study.

Our findings are in line with those of the InChianti Study, which included patients over 65 years old (10). Results on the relationship between vitamin D (and its different forms) and urinary calcium excretion are inconsistent in studies including selected groups of participants. A positive association with 1,25$(OH)_2$D in men and women with urolithiasis (D_2 and D_3 were not differentiated) (24) and 25(OH)D_3 (25) have been described. Another study found a positive association with 1,25$(OH)_2D_3$; it included middle-aged men and compared 109 stone formers with 109 controls (26). In a clinical trial including six men on different calcium diets, urinary calcium excretion was positively associated with 25(OH)D (D_2 and D_3 were not differentiated) (27). Volunteers (men and women included) (28) showed a slight increase in urinary calcium excretion after vitamin D_3 supplementation or exposure to ultraviolet B light. A weak correlation (r=0.27) was found in a study including 160 renal stone formers and 217 nonstone formers (29) between 25(OH)D (D_2 and D_3 were not differentiated) and urinary calcium excretion. In contrast, no association was found in a study including 169 stone formers (11) [25(OH)D was used as the dependent variable, and D_2 and D_3 were not differentiated]. A possible explanation for the sex difference that we observed is sex hormones. A previous clinical trial showed that estrogens have a stimulatory effect on 1α-hydroxylase, increasing the synthesis of 1,25$(OH)_2D_3$ and vitamin D–binding protein but not 25(OH)D_3 (30). Another explanation for the observed sex difference is diet, which was discussed for serum calcium.

Both ACEIs and ARBs were negatively associated with urinary calcium excretion independent of other factors. Whereas these associations were similar in men and women for ACEIs, they were stronger in women than men for ARBs.

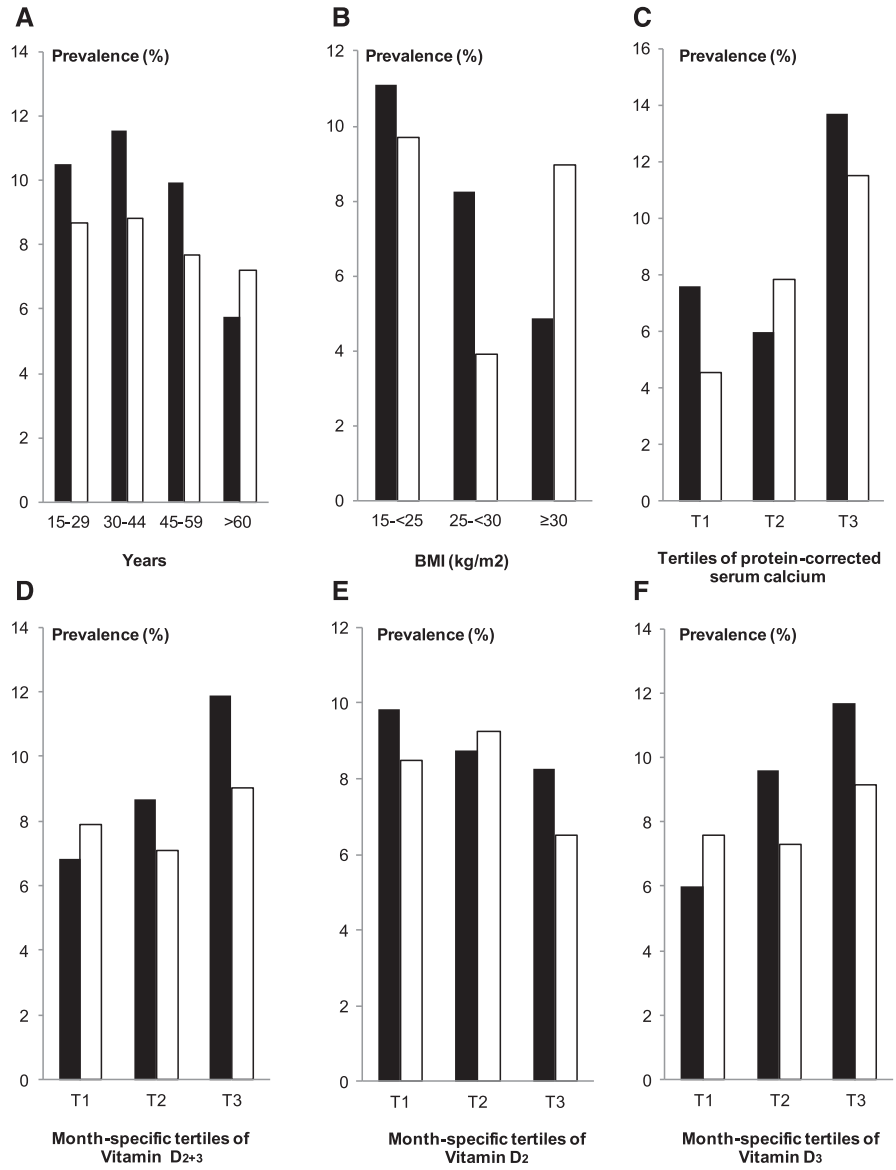

Figure 3. | Prevalence of hypercalciuria (>4 mg/kg per 24 hours) by sex (men are shown as black bars, and women are shown as white bars). Hypercalciuria prevalence by sex across (A) age strata, (B) body mass index (BMI) strata, (C) tertiles of protein-corrected calcium, (D) month-specific tertiles of vitamin D_{2+3}, (E) month-specific tertiles of vitamin D_2, and (F) month-specific tertiles of vitamin D_3.

Although the mechanism underlying the observed associations is unknown, angiotensin type I receptors are present on bone cells, and *in vitro* studies suggest that angiotensin I and II could stimulate bone resorption (31). Also, ACEIs have been associated with reduced fracture risk (32) and reduced calciuria (33,34). By contrast, ACEI, but not ARB, use was associated with a small increase in bone loss restricted to the hip during follow-up in older men (35). Despite some level of inconsistency across studies, currently available evidence suggests that ACEIs and ARBs reduce urinary calcium excretion.

We found a hypercalciuria prevalence of 8.1% in women and 9.0% in men on unrestricted diets using as a cutoff of 4.0 mg/kg per 24 hours. This is lower than was found in prior studies (36). However, these studies were not population based, were of much smaller size, and used a different definition for hypercalciuria. In the literature, hypercalciuria was also defined as >200 mg/24 h (37) in adults on a diet restricted in calcium, phosphorus, and sodium (including men and women nonstone formers, hypercalciuric stone formers, and normocalciuric stone formers). In nonstone-forming women from two different cohorts, the prevalence values of hypercalciuria were 27% (n=99; mean age of 61 years old) and 17% (n=30; mean age of 42 years old) (36). Additionally, in nonstone-forming men, the prevalence was 14% (n=110; mean age of 60 years old). In this study, hypercalciuria was defined as >250 mg/24 h in women and >300 mg/24 h in men on unrestricted diets (36).

The fact that urinary phosphate excretion is higher in men in our study is probably because of higher nutritional intake. Dietary phosphate is known to strongly influence urinary phosphate excretion (38), and men are known to have higher dietary phosphate intake than women (39).

The strengths of this multicentric study are its population-based nature covering the three main linguistic regions of Switzerland, the availability of urinary electrolyte excretion measured in 24-hour urine, and the centralized laboratory measurements. Serum vitamin D was measured using the gold standard method (liquid chromatography-tandem mass spectrometry), and we used month-specific vitamin D tertiles, which are known to reduce seasonal bias. There are some limitations, such as the low participation rate, which limits external validity, and the fact that calcium and vitamin D supplementations used were not specifically detailed from participants, although medication information was taken. Although we cannot exclude that some supplementations have not been reported, this is unlikely to have a strong effect on the results, and this would mainly affect vitamin D_2. The active form of vitamin D, $1,25(OH)_2D$, was not tested. We do not have detailed information on outdoor activities and clothing habits, and therefore, we cannot evaluate the role of exposure to sunlight on the explored associations. Serum phosphate was only available for a subset of participants, and PTH and bone minerals parameters were not available. The absence of a significant association of urinary calcium excretion with menopausal status in the fully adjusted model was unexpected. However, urinary calcium excretion was associated positively with menopausal status when serum calcium, calcium, and vitamin D supplements were not included as covariates in the model.

In conclusion, we found important sex differences in the association of 24-hour urinary calcium excretion with serum calcium and serum $25(OH)D_2$ and/or serum $25(OH)D_3$ in this population-based study. Additional studies are needed to understand the mechanisms underlying these sex differences and particularly, the influence of sex hormones and/or dietary factors on urinary calcium excretion.

Acknowledgments

The authors are grateful to all study participants, study collaborators, Vincent Dudler and Otmar Zoller from the laboratory of the Swiss Federal Office of Public Health, Dr. Tanica Lyngdoh, and Heba Al-Alwan. We thank Pascal Meier for data collection in Valais. The Service of Nephrology and Hypertension and the Institute of Social and Preventive Medicine (Lausanne University Hospital) provided additional logistical support.

The Swiss Study on Salt Intake was supported by Swiss Federal Office of Public Health Contracts N09.004165/404.0101/-2 and 09.005791/414.0000/-74. I.G. is supported by Swiss Foundation for Science Grant 33CM30-124087. D.C. was supported by Swiss National Science Foundation Grant PP00P3_133681. M. Bochud was supported by the Swiss School of Public Health Plus.

Part of this work was presented as a poster at the Annual Meeting of the Swiss Public Health Conference 2013 held August 15 and 16, 2013 in Zurich, Switzerland.

Disclosures

None.

References

1. DeLuca HF: Vitamin D metabolism and function. *Monogr Endocrinol* 13: 1–80, 1979
2. Friedman PA, Gesek FA: Calcium transport in renal epithelial cells. *Am J Physiol* 264: F181–F198, 1993
3. Massry SG, Friedler RM, Coburn JW: Excretion of phosphate and calcium. Physiology of their renal handling and relation to clinical medicine. *Arch Intern Med* 131: 828–859, 1973
4. Norman AW: From vitamin D to hormone D: Fundamentals of the vitamin D endocrine system essential for good health. *Am J Clin Nutr* 88: 491S–499S, 2008
5. Armas LA, Hollis BW, Heaney RP: Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab* 89: 5387–5391, 2004
6. Trang HM, Cole DE, Rubin LA, Pierratos A, Siu S, Vieth R: Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. *Am J Clin Nutr* 68: 854–858, 1998
7. Omdahl JL, Morris HA, May BK: Hydroxylase enzymes of the vitamin D pathway: Expression, function, and regulation. *Annu Rev Nutr* 22: 139–166, 2002
8. Levy FL, Adams-Huet B, Pak CY: Ambulatory evaluation of nephrolithiasis: An update of a 1980 protocol. *Am J Med* 98: 50–59, 1995
9. García-Nieto V, Navarro JF, Monge M, García-Rodríguez VE: Bone mineral density in girls and their mothers with idiopathic hypercalciuria. *Nephron Clin Pract* 94: c89–c93, 2003
10. Vezzoli G, Soldati L, Arcidiacono T, Terranegra A, Biasion R, Russo CR, Lauretani F, Bandinelli S, Bartali B, Cherubini A, Cusi D, Ferrucci L: Urinary calcium is a determinant of bone mineral density in elderly men participating in the InCHIANTI study. *Kidney Int* 67: 2006–2014, 2005
11. Eisner BH, Thavaseelan S, Sheth S, Haleblian G,Pareek G: Relationship between serum vitamin D and 24-hour urine calcium in patients with nephrolithiasis. *Urology* 80: 1007–1010, 2012
12. Guessous I, Dudler V, Glatz N, Theler JM, Zoller O, Paccaud F, Burnier M, Bochud M; Swiss Survey on Salt Group: Vitamin D levels and associated factors: a population-based study in Switzerland. *Swiss Med Wkly* 142: 0, 2012
13. Chappuis A, Bochud M, Glatz N, Vuistiner P, Paccaud F, Burnier M: Swiss Survey on Salt, 2011. Available at: http://www.bag.admin.ch/themen/ernaehrung_bewegung/05190/05294/12869/index.html?lang=fr. Accessed January 24, 2012
14. Parfitt AM: Letter: Correction of plasma calcium measurements. *BMJ* 1: 520, 1974
15. Bruce SJ, Rochat B, Béguin A, Pesse B, Guessous I, Boulat O, Henry H: Analysis and quantification of vitamin D metabolites in serum by ultra-performance liquid chromatography coupled to tandem mass spectrometry and high-resolution mass spectrometry—a method comparison and validation. *Rapid Commun Mass Spectrom* 27: 200–206, 2013
16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150: 604–612, 2009
17. Ghazali S, Barratt TM: Urinary excretion of calcium and magnesium in children. *Arch Dis Child* 49: 97–101, 1974
18. Liebman SE, Taylor JG, Bushinsky DA: Idiopathic hypercalciuria. *Curr Rheumatol Rep* 8: 70–75, 2006
19. Wang Y, Jacobs EJ, McCullough ML, Rodriguez C, Thun MJ, Calle EE, Flanders WD: Comparing methods for accounting for seasonal variability in a biomarker when only a single sample is available: Insights from simulations based on serum 25-hydroxyvitamin d. *Am J Epidemiol* 170: 88–94, 2009
20. Peacock M, Robertson WG, Nordin BE: Relation between serum and urinary calcium with particular reference to parathyroid activity. *Lancet* 1: 384–386, 1969
21. Van Abel M, Hoenderop JG, Dardenne O, St Arnaud R, Van Os CH, Van Leeuwen HJ, Bindels RJ: 1,25-dihydroxyvitamin D(3)-independent stimulatory effect of estrogen on the expression of ECaC1 in the kidney. *J Am Soc Nephrol* 13: 2102–2109, 2002
22. Hsu YJ, Dimke H, Schoeber JP, Hsu SC, Lin SH, Chu P, Hoenderop JG, Bindels RJ: Testosterone increases urinary calcium excretion and inhibits expression of renal calcium transport proteins. *Kidney Int* 77: 601–608, 2010
23. Correale J, Ysrraelit MC, Gaitán MI: Gender differences in 1,25 dihydroxyvitamin D3 immunomodulatory effects in multiple sclerosis patients and healthy subjects. *J Immunol* 185: 4948–4958, 2010

24. Giannini S, Nobile M, Castrignano R, Pati T, Tasca A, Villi G, Pellegrini F, D'Angelo A: Possible link between vitamin D and hyperoxaluria in patients with renal stone disease. *Clin Sci (Lond)* 84: 51–54, 1993
25. Berlin T, Björkhem I, Collste L, Holmberg I, Wijkström H: Relation between hypercalciuria and vitamin D3-status in patients with urolithiasis. *Scand J Urol Nephrol* 16: 269–273, 1982
26. Shakhssalim N, Gilani KR, Parvin M, Torbati PM, Kashi AH, Azadvari M, Golestan B, Basiri A: An assessment of parathyroid hormone, calcitonin, 1,25 (OH)2 vitamin D3, estradiol and testosterone in men with active calcium stone disease and evaluation of its biochemical risk factors. *Urol Res* 39: 1–7, 2011
27. Adams ND, Gray RW, Lemann J Jr., Cheung HS: Effects of calcitriol administration on calcium metabolism healthy men. *Kidney Int* 21: 90–97, 1982
28. Berlin T, Emtestam L, Björkhem I: Studies on the relationship between vitamin D3 status and urinary excretion of calcium in healthy subjects: Effects of increased levels of 25-hydroxyvitamin D3. *Scand J Clin Lab Invest* 46: 723–729, 1986
29. Netelenbos JC, Jongen MJ, van der Vijgh WJ, Lips P, van Ginkel FC: Vitamin D status in urinary calcium stone formation. *Arch Intern Med* 145: 681–684, 1985
30. Aarskog D, Aksnes L, Markestad T, Rødland O: Effect of estrogen on vitamin D metabolism in tall girls. *J Clin Endocrinol Metab* 57: 1155–1158, 1983
31. Hatton R, Stimpel M, Chambers TJ: Angiotensin II is generated from angiotensin I by bone cells and stimulates osteoclastic bone resorption in vitro. *J Endocrinol* 152: 5–10, 1997
32. Rejnmark L, Vestergaard P, Mosekilde L: Treatment with beta-blockers, ACE inhibitors, and calcium-channel blockers is associated with a reduced fracture risk: A nationwide case-control study. *J Hypertens* 24: 581–589, 2006
33. Pérez-Castrillón JL, Silva J, Justo I, Sanz A, Martín-Luquero M, Igea R, Escudero P, Pueyo C, Díaz C, Hernández G, Dueñas A: Effect of quinapril, quinapril-hydrochlorothiazide, and enalapril on the bone mass of hypertensive subjects: Relationship with angiotensin converting enzyme polymorphisms. *Am J Hypertens* 16: 453–459, 2003
34. Puig JG, Mateos FA, Ramos TH, Lavilla MP, Capitán MC, Gil A: Albumin excretion rate and metabolic modifications in patients with essential hypertension. Effects of two angiotensin converting enzyme inhibitors. *Am J Hypertens* 7: 46–51, 1994
35. Kwok T, Leung J, Zhang YF, Bauer D, Ensrud KE, Barrett-Connor E, Leung PC; Osteoporotic Fractures in Men (MrOS) Research Group: Does the use of ACE inhibitors or angiotensin receptor blockers affect bone loss in older men? *Osteoporos Int* 23: 2159–2167, 2012
36. Curhan GC, Willett WC, Speizer FE, Stampfer MJ: Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. *Kidney Int* 59: 2290–2298, 2001
37. Pak CY, Sakhaee K, Moe OW, Poindexter J, Adams-Huet B, Pearle MS, Zerwekh JE, Preminger GM, Wills MR, Breslau NA, Bartter FC, Brater DC, Heller HJ, Odvina CV, Wabner CL, Fordtran JS, Oh M, Garg A, Harvey JA, Alpern RJ, Snyder WH, Peters PC: Defining hypercalciuria in nephrolithiasis. *Kidney Int* 80: 777–782, 2011
38. Vervloet MG, van Ittersum FJ, Büttler RM, Heijboer AC, Blankenstein MA, ter Wee PM: Effects of dietary phosphate and calcium intake on fibroblast growth factor-23. *Clin J Am Soc Nephrol* 6: 383–389, 2011
39. Ervin RB, Wang CY, Wright JD, Kennedy-Stephenson J: Dietary intake of selected minerals for the United States population: 1999-2000. *Adv Data* 341: 1–5, 2004

Received: December 10, 2013 **Accepted:** November 19, 2014

M. Burnier and M. Bochud contributed equally to this work.

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.12511213/-/DCSupplemental.